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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Pharmaceutical Composition for Treating Pigmentation

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Notice: This application is as filed and may therefore contain an incomplete specification.

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PHARMACEUTICAL COMPOSITION FOR TREATING PIGMENTATION

FIELD OF THE INVENTION

This invention relates to a pharmaceutical composition for internal use having a remarkable effect on pigmentation.

BACKGROUND OF THE INVENTION

Pigmentation is considered to ensue from chromatism of melanin in the skin generally caused by heredity, endocrinosis, stimulation by ultraviolet rays of sunlight, skin irritation by photodynamic substances, etc., aggravation of allergodermia, and so on.

Conventionally proposed treatment for pigmentation includes drugs for external use containing hydroquinone, vitamin C derivatives, kojic acid, tranexamic acid, etc. and drugs for internal use containing vitamin C, L-cysteine, glutathione, tranexamic acid, etc. Some of these drugs have already been on the market, but no drugs except hydroquinone preparations shows a sufficient effect in a short time. However, hydroquinone preparations have hardly been used due to their strong side effects.

SUMMARY OF THE INVENTION

Accordingly, an object of the present invention is to provide a pharmaceutical composition for treating pigmentation which is of high safety with freedom from side effects and is expected to produce a sufficient effect through short-term administration.

In the light of the above-mentioned circumstances, the inventors have conducted extensive investigations and, as a result, have found that a combination of tranexamic acid which is noted to have efficacy to some extent when orally administered alone and ascorbic acid or a salt thereof which has no discernible effect when administered alone exerts a synergistically enhanced effect in the treatment of pigmentation and produces high therapeutic effects through short-term administration.

The present invention provides a pigmentation treating pharmaceutical composition for internal use which comprises tranexamic acid and ascorbic acid or a salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

Tranexamic acid, one of the essential ingredients of the pharmaceutical composition of the present invention, is used as an antiplasmin agent and has such very low toxicity as having an LD_{50} of not less than 5 g/kg in dogs (p.o.).

Ascorbic acid, the other ingredient, is also of low toxicity as having an LD_{50} of not less than 5 g/kg in dogs (p.o.). Suitable salts of ascorbic acid include a sodium salt and a calcium salt.

In the pharmaceutical composition of the present invention, ascorbic acid is contained in an amount of 0.3 to 2 parts by weight, preferably 0.5 to 2 parts by weight, per part by weight of tranexamic acid.

The pigmentation treating composition of the present invention is preferably orally administered so that each of tranexamic acid and ascorbic acid or its salt be administered at a dose of from 500 to 1500 mg, particularly from 1000 to 1500 mg, per day in a single dose or several divided doses, particularly three divided doses.

The pigmentation treating composition may be formulated into various preparation forms for oral administration, such as granules, particles, powders, capsules, tablets, solutions, and the like together with a pharmaceutically acceptable carrier.

These preparations can be prepared in a usual manner from the above-mentioned essential ingredients, if necessary in conjunction with adjuvants commonly employed in the art and other drugs.

The present invention is now illustrated in greater detail with reference to Examples, but it should be understood that the present invention is not deemed to be limited thereto.

EXAMPLE 1

Ascorbic acid	1000 mg
Tranexamic acid	1000 mg
Powder sugar	2475 mg
Light anhydrous silicic acid	25 mg

Granules were prepared from the above ingredients in a usual manner and divided into three doses for one day.

TEST EXAMPLE 1

A simple comparative clinical test was carried out as follows.

The medication prepared in Example 1 (A), tranexamic acid alone (B), or ascorbic acid alone (C) was orally administered to patients (all female) suffering from chloasma, a kind of pigmentation, three times a day for 2 months, and the degrees of pigmentation before and after the administration were compared.

Ingredients of Daily Dose (3 doses):

Ingredient	Medication (A)	(B)	(C)
Ascorbic acid	1000 mg	-	1000 mg
Tranexamic acid	1000 mg	1500 mg	-
Powder sugar	2475 mg	2975 mg	3475 mg
Light anhydrous silicic acid	25 mg	25 mg	25 mg

The changes in the clinical picture after the administration of the medication are shown in Tables 1 (group on (A)), 2 (group on (B)), and 3 (group on (C)), and the ameliorating effect of each medication on pigmentation judged from these clinical pictures is shown in Table 4.

The clinical pictures were allocated in accordance with the following five levels.

4: bad (observed through heavy makeup)

3: baddish (covered by heavy makeup)

2: slight (covered by normal makeup)

1: very slight (covered by light makeup)

0: none

In Tables 1 through 3, the degree of improvement was evaluated as follows.

markedly improved: the symptom at any level was improved up to 0 (4→0, 3→0, 2→0, 1→0).

improved: the level of clinical picture was raised by two or three steps (4→2, 4→1, 3→1).

slightly improved: the level of clinical picture was raised by one step (4→3, 3→2, 2→1).

unchanged: the clinical picture was unchanged (4→4, 3→3, 2→2, 1→1).

aggravated: the clinical picture got worse (3→4; 2→3 or 4; 1→2, 3 or 4; 0→1,2,3 or 4)

TABLE 1

Patient Group on (A)

Case	Age	Sites	Degree of Improvement
1	39	forehead, right cheek	markedly improved
2	39	cheeks, below nose	"
3	45	cheeks, below nose	"
4	41	cheeks	improved
5	31	cheeks	"
6	38	cheeks, eyelids	"
7	49	cheeks, eyelids	"
8	40	upper lip	"
9	40	forehead	slightly improved
10	50	right cheek	improved
11	50	cheeks	unchanged
12	47	forehead, cheeks	slightly improved
13	52	cheeks	unchanged
14	45	forehead, cheeks	slightly improved
15	39	cheeks	"
16	40	forehead, cheeks	improved
17	43	forehead, cheeks	slightly improved
18	30	forehead, cheeks	improved
19	41	entire face	"
20	51	cheeks	"

TABLE 2

Patient Group on (B)

Case	Age	Sites	Degree of Improvement
21	45	cheeks	improved
22	53	cheeks	unchanged
23	58	forehead, left cheek	slightly improved
24	43	forehead, cheeks	"
25	35	forehead, cheeks	improved
26	35	cheeks	markedly improved
27	38	cheeks	improved
28	40	cheeks	"
29	50	right cheek	slightly improved
30	39	forehead, cheeks	improved
31	47	forehead, cheeks	unchanged
32	45	cheeks	"
33	39	cheeks	improved
34	40	forehead, cheeks	"
35	37	cheeks	slightly improved
36	30	forehead	improved
37	41	entire face	unchanged
38	33	cheeks	improved
39	40	cheeks	"
40	37	cheeks	slightly improved

TABLE 3

Patient Group on (C)

Case	Age	Sites	Degree of Improvement
41	46	cheeks	unchanged
42	43	cheeks	"
43	38	cheeks	slightly improved
44	49	forehead, cheeks	unchanged
45	40	forehead, cheeks	"
46	37	forehead	slightly improved
47	35	cheeks	"
48	51	entire face	unchanged
49	53	forehead, cheeks	"
50	46	cheeks	improved
51	48	cheeks	unchanged
52	37	right cheek	"
53	33	forehead	slightly improved
54	39	cheeks, below nose	unchanged
55	37	cheeks	improved
56	41	cheeks	unchanged
57	38	cheeks	slightly improved
58	40	left cheek	unchanged
59	42	forehead, cheeks	"
60	39	forehead, cheeks	"

TABLE 4

	Medication (A)	(B)	(C)
Marked Improvement	3	1	0
Improvement	10	10	2
Slight Improvement	5	5	5
No Change	2	4	13
Aggravation	0	0	0
Total	20	20	20
Percent Improvement (%)	65.0 (90.0*)	55.0 (80.0*)	10.0 (35.0*)

Note: * The value in the parentheses is the percent improvement inclusive of slight improvement.

As described and demonstrated above, the pigmentation treating agent according to the present invention has high efficacy in treating pigmentation through short-term oral administration without causing any adverse side effect.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for treating pigmentation for internal use which comprises tranexamic acid and ascorbic acid or a salt thereof both in an effective amount for treating pigmentation and a pharmaceutically acceptable carrier.

2. The pharmaceutical composition according to claim 1, wherein ascorbic acid or a salt thereof is contained in an amount of 0.3 to 2 parts by weight per part by weight of tranexamic acid.

3. The use of tranexamic acid and ascorbic acid or a salt thereof for preparation of a pharmaceutical composition for treating pigmentation.

ABSTRACT OF THE DISCLOSURE

A pharmaceutical composition for treating pigmentation for internal use which contains tranexamic acid and ascorbic acid or a salt thereof is disclosed. The composition is useful for treating pigmentation in a short time when orally administered.